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SIDE EFFECTS AND EXPERIENCES OF DOPING WITH ANABOLIC ANDROGENIC STEROIDS IN MEN AND WOMEN

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Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-033-9
Cover illustration: Tove Hennix
Language editing in English: Margaret Myers, Alerto Consulting

SIDE EFFECTS AND EXPERIENCES OF DOPING WITH ANABOLIC ANDROGENIC STEROIDS IN MEN AND WOMEN
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at H1 Röd, Alfred Nobels allé 23, Friday, May 21th 2021 at 09:30 a.m.

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Anabola androgena steroider (AAS) används främst av estetiska och prestationsförhöjande orsaker. Användningen av AAS är ett folkhälsoproblem och en angelägenhet i samhället på grund av fysiska och psykiska biverkningar. Män och kvinnor använder AAS trots deras kända negativa effekter och okända långvariga risker.

Studiernas ansatser har dels varit kvantitativa (**studierna I, II, III, IV***)* och dels kvalitativa (**studierna V och VI**). Syftet med denna avhandling var huvudsakligen att:

- studera somatiska och psykiatriska biverkningar av AAS
- beskriva användarmönster och identifiera självrapporterade dopingsubstanser i urin
- beskriva levda erfarenheter från användning av AAS

AAS användes för att öka muskelmassan, prestera bättre och minska i fettmängd. Männen ville skapa den perfekta manliga fysiken medan kvinnorna upplevde att deras kroppar inte var tillräckligt perfekta. Kvinnorna initierades till AAS av en man i nära förhållande medan män ofta upplevde ett grupptryck från vänner som handlade om att inte ”halka” efter i träningsresultaten. Förstahandsvalet av AAS substans skiljde sig åt mellan könen. Männen använde AAS i högre doser och det var vanligare att de använde injektionspreparat. Både män och kvinnor rapporterade typiska klassiska biverkningar av AAS. De uttryckte en oro över upplevda biverkningar men med skillnaden att kvinnor kontaktade sjukvården i ett tidigare skede än män. Få ville dock erhålla professionell hjälp för att avsluta sin användning. Individer som diagnostiserats med en personlighetsstörning uppvisade en signifikant ökad risk att rapportera aggressivitet, självmordstankar/försök och kriminalitet. Män med en pågående användning av AAS hade höga hematokrit- och hemoglobinvärden och rubbade kolesterolvärden, vilket tillsammans med ett högt blodtryck kan vara en riskfaktor för hjärt- och kärlsjukdomar. En enda dos av AAS substansen nandrolon visade sig öka den totala kolesterolnivån och gav oss en indikation på att även låga doser kan vara en bidragande riskfaktor.

Av de manliga testosteronanvändarna uppnådde 82 % en testosteron/epitestosteron kvot över 4 vilket är gränsen för ett positivt dopningstest hos idrottare. Kvinnliga användare av testosterongel nådde dock inte denna gräns. Så många som 50 % av de manliga testosteronanvändarna och 100 % av de kvinnliga användarna av AAS undslapp ett positivt dopingtest eftersom gränsvärdet för ett positivt prov i samhället är högre satt (≥10). Detta

indikerar att AAS användare utanför idrotten som endast använder testosteron som dopningsmedel inte lika ofta blir positiva i dopingtest.

Män och kvinnors användning av AAS är ett komplext fenomen. Det är en existentiell utmaning att nå den perfekta kroppen. Missnöjet med kroppen skapar ångest, som bemästras med hård träning, strikt kost och AAS. Låg självkänsla kompenseras genom självkontroll, disciplin och prestation. Kvinnor upplever en känsla av stolthet när de lyckas med sina prestationer. Detta är deras drivkraft, som utlöser spänningar mellan lidande och framgång. En mödosam strävan finns att balansera biverkningar av preparatets effekt och den eftersträvansvärda kvinnligheten. Den perfekt förvärvade manliga kroppen är skör ur både ett existentiellt och biologiskt perspektiv. Den perfekta självbilden kan lätt raseras av motgångar. Existensen kan sättas i gungning om användningen av AAS avslöjas eller om kroppen sviker på grund av sjukdom.

ABSTRACT

Anabolic androgenic steroids (AAS) are mainly used in non-medical conditions for aesthetic and performance- enhancing purposes. The use of AAS is a growing public health problem and a concern in society due to side effects. Men and women use AAS despite their known negative effects and unknown long-term risks.

The research in this thesis aimed to study somatic and psychiatric side effects, describe patterns of use, compare self-reported doping agent use with urine test results and to describe AAS users' lived experiences. The approaches in this thesis have been both quantitative (**Studies I-IV**) and qualitative (**Studies V-VI**) and were focused on use of AAS outside the field of sports.

Study I was an experimental study and included eleven healthy male volunteers administered with a single dose of nandrolone. The aim was to study endocrine and cardiovascular effects. The results showed that luteinising hormone, follicle stimulating hormone and testosterone were suppressed for 14 days after administration. Cholesterol and an enzyme involved in the cholesterol synthesis were increased and hence AAS may be a risk factor for cardiovascular diseases even in low doses.

Studies II and III were descriptive studies with eight women and fifty-six men who contacted healthcare (Anti-Doping Hot-Line) on their own initiative. The aim was to identify the pattern of doping agent use in women and compare with similar data reported in men. We also aimed to identify psychiatric and personality disorders and to measure anxiety and depression in men using Structured Clinical Interviews Diagnosis -I and -II, the Brief Scale for Anxiety and the Montgomery Asberg Depression Rating Scale. The participants were interviewed about demographics, details of their AAS use and other co-used substances. They were also asked about motives, side effects they experienced and family background.

Both men and women expressed a concern for side effects but there were very few who wanted professional help to terminate their AAS use. Classical side effects of AAS were reported and women contacted healthcare at an earlier stage of use. Women were introduced to AAS by a man in a close relationship. Male individuals diagnosed with a personality disorder showed a significantly increased risk of reporting aggressive feelings/behaviour, suicidal thoughts/attempts and criminality. It was more common that men used injections, higher doses of AAS and several different AAS substances per cycle compared with women.

Study IV was an experimental and descriptive study with thirty men and six women who self-reported use of AAS and other performance-enhancing substances within the past year. Our aim was to identify which doping agents could be detected in doping test. The results showed that as many as 50% and 100 % respectively of current male and female testosterone users may escape a doping test. This indicates that AAS users outside the field of sports using only testosterone as a doping agent may not be identified by the routine tests currently used. In men, luteinising hormone and follicle stimulating hormone were normalised within 6-12 months. Haematocrit and haemoglobin values were shown to be high in male current users compared with previous users whereas all women displayed normal values. Thus, cessation of AAS use may reduce the risk of cardiovascular diseases relatively fast.

Studies V and VI were qualitative studies with twelve women and twelve men using AAS. The studies applied a phenomenological approach aimed to describe AAS users' lived experiences of using AAS. Our aim was to deepen the understanding about women's and men's use of AAS. The results showed that it is an existential challenge to achieve the perfect body. Body dissatisfaction were mastered by hard training, strict diet and the use of AAS. Low self-esteem is compensated for by self-control, discipline and performance. For women it is an arduous endeavour to balance the substances' side effects with desired femininity. For men the new self-identity stimulates respect by being impressive, prominent and dominant. The use of AAS means living with lies and the fear of being discovered, which may lead to consequences and feelings of not being genuine. The built-up body is fragile from both an existential and a biological perspective, self-esteem can quickly be destroyed in the absence of confirmation and acceptance from others or the substances may damage the body in the form of side effects.

Conclusions and reflection: Our studies show that AAS use is associated with many somatic and psychiatric side effects. However, regardless of the perceived side effects, many choose to continue with their AAS use. The fact that the use of AAS is illegal does not prevent those who want to from achieving their goals. A non-judgemental attitude would facilitate the meeting between AAS users and healthcare as it could lead to users experiencing trust and security and would encourage open and honest communication.

LIST OF SCIENTIFIC PAPERS

The thesis is based on the following six studies.

I. Gårevik N, **Börjesson A**, Choong E, Ekström L, Lehtihet M. Impact of single-dose nandrolone decanoate on gonadotropins, blood lipids and HMG CoA reductase in healthy men. *Andrologia.* 2015 Aug 10. doi: 10:1111/and.12488.

II. **Börjesson A**, Gårevik N, Dahl ML, Rane A, Ekström L. Recruitment to doping and help-seeking behavior of eight female AAS users. *Subst Abuse Treat Prev Policy*. 2016 Mar 5. doi: 10.1186/s13011-016-0056-3.

III. **Börjesson A**, Möller C, Hagelin A, Vicente V, Rane A, Lehtihet M, Dahl ML, Gårevik N, Ekström L. Male anabolic androgenic steroid users with personality disorders report more aggressive feelings, suicidal thoughts, and criminality. *Medicina.* 2020 May 26. doi:10.3390/medicina56060265

IV. **Börjesson A**, Lehtihet M, Andersson A, Dahl ML, Vicente V, Ericsson M, Ekström L. Studies of athlete biological passport biomarkers and clinical parameters in male and female users of anabolic androgenic steroids and other doping agents. *Drug Test Anal.* 2020 Jan 7. doi: 10.1002/dta.2763.

V. **Börjesson A**, Ekebergh M, Dahl ML, Ekström L, Lehtihet M, Vicente V. Women's experiences of using anabolic androgenic steroids. *In manuscript.*

VI. **Börjesson A**, Ekebergh M, Lehtihet M, Dahl ML, Ekström L, Vicente V. Men's experiences of using anabolic androgenic steroids. *In manuscript.*

Scientific articles not included in the thesis:

Lehtihet M, Andersson A, **Börjesson A**, Schulze J, Rane A, Ericsson M, Ekström L. Codeine influences the serum and urinary profile of endogenous androgens but does not interact with the excretion rate of administered testosterone. *Drug Test Anal.* 2018 Apr 10. doi: 10.1002/dta.2301.

Mullen J, **Börjesson A**, Hopcraft O, Schulze JJ, Ericsson M, Rane A, Lehtihet M, Ekström L. Sensitivity of doping biomarkers after administration of a single dose testosterone gel. *Drug Test Anal.* 2018 May 10. doi: 10.1002/dta.2341.

CONTENTS

LIST OF ABBREVIATIONS

AAS	Anabolic Androgenic Steroids
ABP	Athlete Biological Passport
APO-A1	Apolipoprotein A1
Apo-B	Apolipoprotein B
AR	Androgen receptor
BSA	Brief Scale for Anxiety
CPRS	Comprehensive Psychopathological Rating Scale
DHT	Dihydrotestosterone
EAAS	Endogenous Anabolic Androgenic Steroids
FSH	Follicle stimulating hormone
GC-MS/MS	Gas chromatography-tandem mass spectrometry
GC-C-IRMS	Gas chromatography-combustion-isotope-ratio mass spectrometry
GH	Growth hormone
Hb	Haemoglobin
hCG	Human chorionic gonadotropin
HCT	Haematocrit
HDL	High-density lipoprotein
HMGCR	3-hydroxy-3 methyl-glutaryl-CoA reductase
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low-density lipoprotein
LH	Luteinising hormone
MD	Muscle Dysmorphia
mRNA	Messenger RNA
PD	Personality Disorder
PES	Performance Enhancing Substances

RecGH	Recombinant growth hormone
RLR	Reflective Lifeworld Research
SCID	Structured Clinical Interview Diagnosis
T/E	Testosterone to epitestosterone ratio
UGT	Uridine diphospho-glucuronosyl transferase
WADA	World Anti-Doping Agency

PREFACE

In my work as a nurse, I feel a certain frustration that users of anabolic androgenic steroids (AAS) do not dare to seek medical care due to concern about how they will be treated and for fear of not getting help with their issues. They may have gathered the courage to seek help but had a negative experience that makes them never want to do it again. They never dare to take that step again.

I work at the Anti-Doping Hot-Line which is an organisation that answers questions from the public about AAS. In our telephone counselling service, we often hear stories from when AAS users have tried to seek help: *"We do not work with that"; "You must blame yourself"; "Your side effects will surely disappear with time"; or "Don't think we will prescribe testosterone for you".*

Men's and women's most common question to the Anti-Doping Hot-Line is about side effects. AAS users are often worried that the side effects will never disappear. The problems vary in size, from minor issues to matters occupying the individual's entire life: "*Have I destroyed my hormone production?"; "My clitoris has grown"; Will I ever have children?"; "My voice has changed"; or "I have suicidal thoughts".*

Many AAS users seek help online in fora, which need not be wrong per se, but incorrect and even harmful advice exists so users need to be critical of what they read. An anonymous telephone counselling service like ours means that those who contact us do not have to worry to the same extent about how they will be treated or if they will be reported to the police. They can be open and honest about their use of AAS. We believe that the trust in us as an organisation has increased over the years and our experience is that to be able to reach AAS users, it is important not to judge and spread intimidation "propaganda".

The use of anabolic androgenic steroids is not a priority area in society when it comes to research, treatment or information dissemination. I am so grateful that it has been possible to carry out the research in this thesis and that the Anti-Doping Hot-Line has continued to exist thanks to the Department of Clinical Pharmacology. This thesis provides understanding and knowledge which is important in order to be able to meet men and women in their fears and difficulties.

1 INTRODUCTION

1.1 ANABOLIC ANDROGENIC STEROIDS

1.1.1 History

For a long time, there has been a quest for performance-enhancing effects. The ancient Greeks increased their performance by using herbs and fungi, many hallucinogenic. Roman gladiators readily gulped stimulants, including caffeine and strychnine. Athletes in the Olympic Games (BC) prepared themselves by eating bread with spices from the juice of the opium poppy to make themselves strong, brave and fast (1). In the 1870s, the physician Charles Edouard Brown-Séquard experimented on himself by injecting extracts from the testicles of dogs and guinea pigs, hoping to experience a rejuvenating effect. After the injections, Edouard Brown-Séquard described having recovered his strength and stamina and his report inspired (2). In 1935, testosterone was isolated and a few years later, methods were published for the synthesis of testosterone (3, 4). The use of anabolic androgenic steroids (AAS) entered elite sports but for many years it was claimed that AAS simply did not work (5, 6). However, the athlete's own experience told another story (7) and the anabolic effects were later proved (8, 9). During the 1950s and 1960s variations of the testosterone molecule were synthesised with the aim of creating a steroid with minimal side effects and greater anabolic effect (10), but without success (11).

AAS were first banned by International Olympic Committee in 1968 and after that it did not take long before AAS use had spread into bodybuilding and the general population (6).

1.1.2 Testosterone and other AAS

Testosterone is the most important male hormone (androgen) which mainly develops the male sex and masculinity. However, testosterone is important for women as well, for their psychological well-being, sexual function, muscle mass and bone density, although women's production is 10 times less than men's (12). Testosterone is clinically used for androgen replacement therapy in men with androgen deficiency (13).

All AAS are chemical modifications of testosterone developed in an attempt to acquire a more effective drug with fewer side effects (5) but also to avoid detection in urine testing (11). High doses of AAS can greatly increase strength, muscle and fat-free mass, especially when combined with strength training (8, 14). Further positive effects reported by users are increased energy and libido (15) and a faster recovery between recurring workouts (11). AAS has existed since the 1940s as a treatment for trauma, burns and debilitating illnesses, but

today they are used to a very limited extent and with great caution due to their negative effects (11, 16).

The androgenic and anabolic effects that are obtained when using AAS originates mainly from activating the androgen receptor (AR). The organs and target tissues determine the biological effect (17). Dihydrotestosterone (DHT) is a metabolite of testosterone that has a higher affinity with AR than testosterone and is formed by a conversion with help from the enzyme, 5α-reductase. This enzymatic activation is important for the function of testicles, skin, prostate, brain, bones and adipose tissue. DHT is responsible for many of the unwanted androgenic side effects e.g. hair loss, acne and prostate enlargement. The anabolic effects such as induction of protein synthesis, muscle fibre development, erythropoiesis, stimulation and inhibition of bone growth do not require as much of this enzyme activity (17).

1.1.3 Motives for AAS use

AAS use in men is predominantly motivated by the desire for the anabolic effect (15, 18) in particular to increase muscle mass and strength (15, 19-21). Several studies have shown that improvement in body image and appearance is important for initiating an AAS use. Other motives are low self-esteem, curiosity, desire for increased braveness or criminality (20, 22-24). Moving beyond what has been achieved by training "naturally" has also been seen as a motivation (25). The majority of male users define themselves as recreational exercisers or bodybuilders (20). In women, sports performance is given as a reason for using AAS (26) and the use is associated with sporting activity, body-building and weightlifting (27). However, more studies of women are needed to be able to understand their motives.

Muscle Dysmorphia (MD) is a subcategory of body dysmorphic disorder and includes a pathological preoccupation with muscularity (28), focused on dissatisfaction and the idea that the body is insufficiently muscular (29). It has been found that MD does occur in AAS using men (30). Male bodybuilders report a greater incidence of MD than non-bodybuilders resistance trainers (31, 32). There is no information about MD in AAS using women except that they do not feel lean and muscular enough (27).

1.1.4 Patterns of use

AAS are generally administered orally or parenterally and are often taken in supraphysiological doses (33, 34), up to 100 times or higher than the medical replacement dosages (35, 36). Users typically take steroids in cycles (11, 37), often repeated a couple of times each year, but longer periods of continuous use also occur. Multiple AAS preparations e.g. a combination of two or more steroids are often used at the same time, so called stacking

(11). The supposed reason for using several types of AAS is to maximise AR binding and to activate multiple steroid receptor sites (38). A majority of males use injectable AAS formulations (39), whereas females prefer oral use as their main AAS administration route (19). Women generally take fewer AAS substances and lower doses than men (26). Notably, most studies are based on self-reported questionnaires. In Studies II, III and IV, the use pattern has been assessed in confirmed AAS users.

It is common that users consistently use a wide range of additional drugs in combination with several types of AAS (39). These substances are used to increase desired effects and/or to minimise unwanted effects. Performance-enhancing drugs (PES) and even "classic" drugs are examples of this (20, 33, 34, 40, 41). Growth hormone (GH) is used for anabolic and fat-burning reasons (42). Ephedrine and clenbuterol reduce body fat and the latter also has anabolic effects (43-45). Prescription drugs are used for a variety of purposes, commonly for recreational or relaxation purposes or to combat side effects (39, 46). These include hypnotics, analgesics, potency-enhancing drugs, sedatives, antidepressants, antianxiety drugs and diuretics. Anti-oestrogens and aromatase inhibitors are used to antagonise the oestrogenic side-effects (47) with the intention of reducing the risk of gynaecomastia, maintaining testicular volume, and promoting the endogenous production of testosterone after completing a cycle. These drugs are often used for prophylactic reasons despite the absence of any symptoms.

A co-use of cannabis (48, 49) and amphetamine has been reported (48). Cannabis helps users to wind down and relax after training sessions, while amphetamine is used to lose or maintain weight, to become more alert and to train harder. AAS users are more likely to use alcohol (50), a phenomenon that has also been seen in AAS-treated rats (51).

AAS users also commonly take dietary supplements (41) as a complement to their regular diet, to gain muscle mass and/or to reduce body fat.

Figure 1. The AAS user often uses other substances in addition to AAS.

1.1.5 Side effects

Side effects of AAS may affect both men and women i.e. the desired effects can be followed by less desirable effects. Some of the side effects are mild and reversible but others can be irreversible and more serious, especially among women. Since doping agents are often obtained from illegal sources, purchased online (22, 39), or from fellow users or gym staff (25), it is not possible to be sure of their content, quality and sterility (39) which can cause unpleasant surprises. The risks for side effects increase with higher doses and longer duration of use (52, 53). The type of drug and the individual sensitivity of response are also of importance (17).

Typical physical side effects of AAS in men, reviewed by (36), include gynaecomastia, potency problems and acne. Side effects in women include enlargement of the clitoris, voice change, acne, increased body hair, reduced breasts, swollen body and menstrual disorders (21, 27, 38, 54, 55).

An association has been seen with a variety of psychiatric complications (56). Typical psychiatric symptoms of AAS in men, reviewed by (36) include depression, aggressiveness, anxiety, sleeping disorders, and mood disturbances. Aggression, depression and other mood disturbances are also reported by women (21, 27, 38, 54, 55).

AAS use may increase the risk of cardiovascular complications (57, 58), including hypertension (59) and disturbances in the cholesterol profile (60). The “good” cholesterol HDL decreases while the “bad” cholesterol LDL increases, which is a risk marker for coronary artery disease (61).

Cholesterol levels in the body derive from two sources, dietary intake and biosynthesis. Most of the cholesterol utilised by healthy adults is synthesised in the liver. The most important enzyme in cholesterol synthesis is HMG-CoA-reductase (HMGCR). This enzyme is inhibited by statins, a drug family commonly used for its cholesterol-lowering effect. HMGCR seems to be upregulated by testosterone at least in vitro (62) while no in vivo studies are available. In **Study I**, the effect of nandrolone on HMGCR mRNA has been investigated in vivo.

Cardiovascular consequences of AAS have received much attention due to case reports of death associated with intake, also, cardiac arrest and myocardial infarction (63, 64). Elevated haematocrit (HCT) values may be a risk factor for thrombotic events in AAS users (59). Only one single dose of 500 mg testosterone in healthy volunteers has been shown to increase Haemoglobin (Hb) (62) in males. A cessation of AAS use can lead to a decrease in HCT and Hb in men (65). Studies on haematological parameters in women using AAS are sparse, and this has been investigated in **Studies II and IV**.

Lutenising hormone (LH) and follicle stimulating hormone (FSH) are central to reproduction and secreted from the pituitary gland in the brain (see Figure 2). AAS users have been shown to have a disturbed endocrine profile (60, 66) and their endocrine hormones (LH and FSH) can be suppressed for long periods (60) which may lead to reduced fertility (67). After an AAS cycle when the body has reduced the production of testosterone, impotence and loss of libido can be troublesome. In **Study I** and **Study IV**, AAS mediated effects on the endocrine hormones have been evaluated and the endocrine biomarkers in relation to last intake were studied.

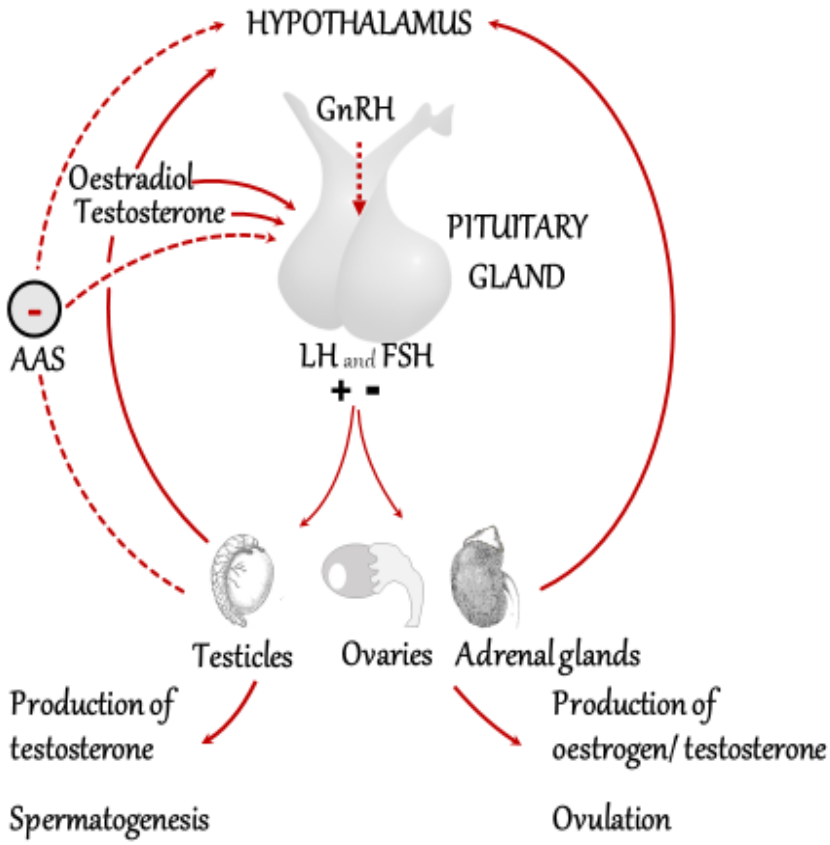

Figure 2. The regulatory feedback mechanism of steroids. The hypothalamus and pituitary gland indirectly regulate the body´s own testosterone secretion. The hypothalamus produces gonadotropin-releasing hormone (GnRH). GnRH stimulates the pituitary gland to produce luteinising hormone (LH) and follicle stimulating hormone (FSH). LH and FSH regulate the production of the sex hormones in the gonads. Through this system, the amount of testosterone can be "read" in the blood and as a result the secretion can be regulated, so-called negative feedback. The dotted line represents the negative feedback mechanism that occurs when using AAS. Hypothalamic GnRH and the pituitary gland`s production of LH and FSH inhibit which leads to reduced production of endogenous testosterone and spermatogenesis. This feedback mechanism is not sufficiently studied in women using AAS.

1.1.6 Doping test

The use of AAS is banned both in sports (68) and in Swedish society (69). In fact, Sweden has the world´s most restrictive law regarding AAS. The use of steroids is prohibited for medical and ethical reasons. It is also illegal to import, sell, possess, manufacture, dispense and purchase AAS.

The World Anti-Doping Agency's (WADA) mission is to lead a collaborative worldwide movement for doping-free sport (70). They establish the international regulatory framework that applies to athletes worldwide. The prohibited list includes a number of substances that are performance-enhancing, a potential health risk and a violation to the sport. AAS fulfil all three criteria. Analysing and verifying AAS are important functions according to Swedish law and sports rules.

For analysing endogenously administered anabolic androgenic steroids (EAAS) such as testosterone, the testosterone/epistestosterone (T/E) ratio is the most important biomarker. When testosterone is administered, testosterone increases and epitestosterone decreases in men (71). The intra-individual variation is low i.e. the T/E ratio is quite stable, at least in men (17). A cut-off T/E ratio of 4 is set by WADA as being "suspicious" for EAAS doping (technical document EAAS 2018). Outside the WADA community, higher T/E cut-offs are employed, i.e. T/E ≥ 10 at our Drug Abuse Laboratory (based on (72)). This is to circumvent false positive results since some individuals naturally have T/E above 4. A previous study indicates that many men using testosterone may escape a T/E test (60). In **Study IV**, the T/E ratio in relation to testosterone intake was studied in men and women.

1.1.6.1 Genetic variability and Athlete Biological Passport

Uridine diphospho-glucuronosyl transferase 2B17 (UGT2B17) is the major enzyme involved in converting testosterone to a more water-soluble metabolite, by adding a glucuronide group. It has been shown that deletion polymorphism of the gene UGT2B17 affects the excretion rate of testosterone in urine (73). In the absence of the gene (deletion/deletion), only a negligible amount of testosterone can be measured in the urine. How common the lack of this gene is differs between ethnic populations (73). This polymorphism limits the T/E ratio test, particularly so when the Athlete Biological Passport (ABP) approach is not used (71).

WADA implemented the steroid module of ABP in 2014. ABP means that the athlete's own individual values constitute the reference range and if a value falls outside the individual reference range, it results in an atypical finding. (74).

In the steroid module, five ratios of six urinary steroid metabolites are monitored, T/E ratio being the most sensitive for testosterone detection. Using ABP makes it easier to discover the use of testosterone compared with population-based ratios because more samples result in a narrower reference range (75).

2 RESEARCH AIMS

The general aims of this thesis are to:

- Study the somatic and psychiatric side effects of AAS
- Describe patterns of use and identify self-reported doping agents in urine
- Describe lived experiences of using AAS

This has been done by the contributions of the specific aims of the six Studies (**I-VI**):

I. Investigate how a single dose of 150 mg of nandrolone affects the sex hormones, blood lipids and gene expression of the key enzyme in cholesterol production HMG CoA reductase, in healthy volunteers.

II. Identify the pattern of doping agent use in eight female cases and compare them with similar data reported from men.

III. Identify psychiatric symptoms and disorders and to measure anxiety and depression in men using AAS.

IV. Identify which doping agents can be detected in men and women self-reporting AAS use. Moreover, haematological parameters, cholesterol profile and endocrine status were determined and analysed in relation to time from the last intake.

V. Deepen the knowledge and understanding of women's experiences of using AAS by using the lifeworld perspective.

VI. Deepen the knowledge and understanding of men's experiences of using AAS by using the lifeworld perspective.

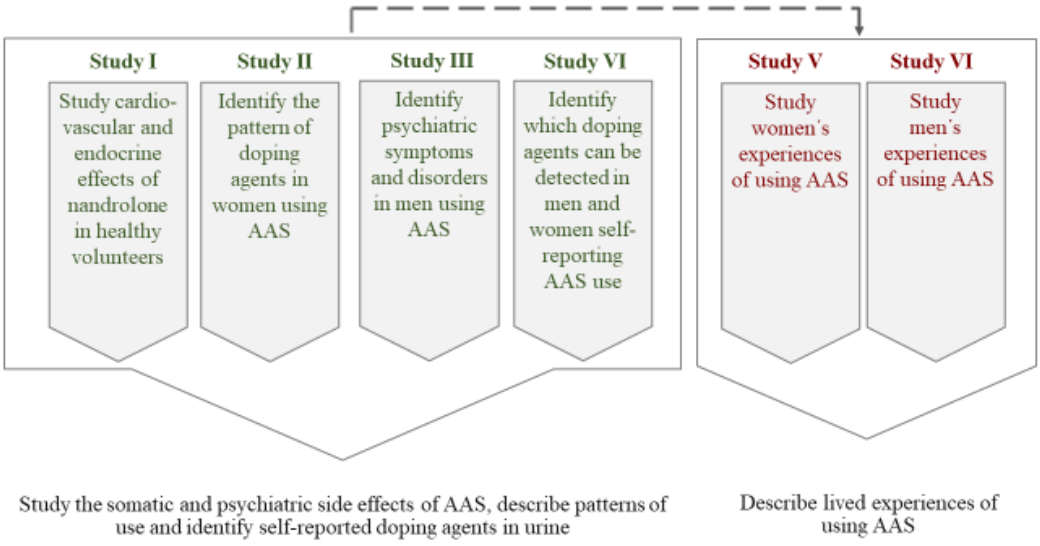

Figure 3. The specific aims of the studies

3 MATERIALS AND METHODS

The studies in this thesis are based on both quantitative and qualitative studies. This chapter provides a broader overview of methods used, and for more detailed method sections I refer to each article. In the following section, the design and method for data collection and analysis for the six Studies (**I-VI**) are presented. Table 1 below gives a summary of the studies in this thesis.

Study	Study design	Year of data collection	Number of participants	Gender	Age
I	**Experimental**	**2014**	**11**	♂	**29 - 46**
II	**Descriptive**	**1998 – 2004**	**8**	♀	**16 - 31**
III	**Descriptive**	**1998 – 2002**	**56**	♂	**15 - 56**
IV	**Experimental** **Descriptive**	**2016 – 2017**	**36**	♂ ♀	**21 - 66**
V	**Qualitative**	**2017 – 2019**	**12**	♀	**21 - 56**
VI	**Qualitative**	**2017 – 2019**	**12**	♂	**23 - 65**

3.1 DATA COLLECTION

3.1.1 Studies I-VI

Study I

In this study, eleven healthy male volunteers were given a single intramuscular dose of 150 mg nandrolone decanoate (ND) of Deca Durabol ®, Organon. All participants underwent a medical examination that included laboratory tests before enrolment. The participants were negative in screening tests for illegal drugs and were not using any medication or dietary supplements. Blood samples were collected prior to ND administration (day 0) and days 4 and 14 post-dose.

Studies II and III

In these studies, eight women and fifty-six men were interviewed by a study nurse about demographics, details of their AAS use and other co-used substances. Further they were asked about their motives for using AAS, side effects they experienced, exercise patterns and family backgrounds. In **Study II**, blood samples were collected in order to analyse cholesterol profile and Hb. In **Study III** structured Clinical Interviews Diagnosis -I and II (SCID) were performed to diagnose psychiatric and personality disorders. The Brief Scale for Anxiety (BSA) and Montgomery Asberg Depression Rating Scale (MADRS) (subscales from the Comprehensive Psychopathological Rating Scale) were used to measure changes in anxiety and depression. Urine samples were collected (**Studies II and III**) for analysis of AAS, other doping agents and drugs of abuse.

Study IV

In this study, thirty men and six women reported their use in the past year of performance enhancing substances (PES) and all other drugs used by completing an anonymous questionnaire. Information requested included: age, gender, PES and other drugs used, doses, lengths of cycles. Moreover, they were asked about how many years they had been using PES and the number of AAS intakes per year. Self-reported doping agents were compared with results of urine analysis. Blood samples were collected in order to analyse lipids, hormones and haematological parameters.

Studies V and VI

In these studies, semi-structured in-depth lifeworld interviews with current or former AAS users (twelve women and twelve men) were conducted. A lifeworld interview is a

phenomenon-orientated data collection method that aims to get rich meaning descriptions of a phenomenon. The interview consisted of open questions to give the informants the opportunity to reflect on their experiences of using AAS. Each interview started with an initial question: "How is it to use anabolic androgenic steroids?" Open follow-up questions were asked (e.g., how do you mean, can you describe more?) to capture the individual´s perception and to gain deeper insight into the phenomenon. The interviews lasted between 45 to 90 minutes, were tape-recorded and transcribed verbatim.

3.1.2 Recruitment

The participants in **Study I** were contacted by a study nurse as they had previously participated in studies at our department. The recruitment of the participants in **Studies II, III, IV, V, VI** was carried out through the Anti-Doping Hot-Line, Department of Clinical Pharmacology, Karolinska University Hospital, Sweden. The Anti-Doping Hot-Line is an anonymous telephone counselling service for people concerned or affected by the non-medical use of AAS. The Anti-Doping Hot-Line service was established in 1993 and is managed by health personnel. All men and women in **Studies II** and **III** contacted the Anti-Doping Hot-Line themselves, on their own initiative. In **Studies IV, V** and **VI,** the participants were recruited via the Anti-Doping Hot-Line but also via the "snowball sampling technique". Snowball sampling is a method for studying the structure of social networks in hard-to-reach populations (76). The method involves an initial contact ("gate-keeper") to get in touch with people, in this case AAS users, who in turn can generate new informants. Thus, the sample group appears to grow like a rolling snowball.

The number of individuals is low (**Study II, III, IV**) compared with other studies based on questionnaire surveys. AAS users are difficult to recruit and the recruitment process turned out to be much more difficult than expected. Based on our experience, we know that this is a hard-to-reach population, which is consistently seen in other studies as well. The recruitment of women is even more difficult since AAS use is less common in women. One of the main causes is probably the Swedish legislation. It does not simply forbid the possession and distribution of AAS, but also the presence of these substances in the body (69).

3.2 DATA ANALYSIS

3.2.1 Sample analyses

All individuals in **Studies II, III** and **IV** were screened for AAS, PES and drugs of abuse to be able to compare the self-reported intake and findings in urine. To stop using AAS and drugs was also a prerequisite for participating in studies **II** and **III** and therefore screening was necessary.

AAS were analysed with Gas chromatography- tandem Mass spectrometry (GC-MS/MS) and Liquid chromatography-mass spectrometry (LC-MS/MS). All the urine samples were analysed by the WADA accredited Doping Control Laboratory at Karolinska University Hospital. AAS and other doping agents were screened by detecting the parent compounds or their long-term metabolites.

In **Studies I and IV**, serum was analysed for sex hormones (testosterone, LH, FSH) and lipids (total cholesterol, LDL, HDL, ApoA, ApoB). The samples were analysed by accredited routine methods at the Department of Clinical Chemistry, Karolinska University Hospital and were carried out using different immuno-based assays whereas the lipids were determined with LC-MS methods.

Furthermore, in **Study IV** additional serum concentrations of DHT and testosterone, and their sulfate (S) and glucuronide (G) conjugates were analysed by ultra-high-performance liquid chromatography coupled to high resolution mass spectrometric detection (UHPLC-HRMS) as described (77). GH was analysed with the GH isoform test at the Doping Control Laboratory. Hb and HCT in **Study II** were analysed by routine methods at Department of Clinical Chemistry, whereas in **Study IV** the haematological parameters were analysed using the Fluorescence Flow Cytometry (Sysmex) technique.

3.2.1.1 Genetic analyses

In **Studies I** and **IV,** genetic analyses were carried out. In **Study I,** the mRNA expression of HMGCR in lymphocytes was analysed using real-time PCR. The HMGCR was normalised against a reference gene GAPDH (Human GAPDH Endogenous Control, Life Technologies) to account for differences in template (cDNA) concentrations and presence of inhibitory substances.

UGT2B17 gene deletion analyses in **Study IV** were carried out by real-time PCR. The samples with PCR-signal in the UGT2B17 specific analysis were identified as UGT2B17 positive (homozygous and heterozygous for the gene insertion). Those without UGT2B17

signal were classified as homozygous for the deletion allele after being tested positive on a control gene (albumin).

3.2.2 Structured Clinical Interview Diagnosis

In **Study III**, SCID, psychiatric semi-structured interviews were performed at one time point by a psychiatrist. SCID are employed for diagnosing current or past psychiatric conditions (78). SCID I is used as a support for diagnosing mental symptoms including abuse or addiction to alcohol or other substances and SCID II is used to diagnose PD. Diagnoses are made according to the diagnostic criteria published in the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM) (79). The DSM is an instrument that classifies mental disorders and is used as a support to improve diagnoses, treatment, and research.

3.2.3 Depression and Anxiety Scales

In **Study III,** Comprehensive Psychopathological Rating Scale (CPRS), semi-structured interviews were conducted by trained nurses at the first visit and in month six. The total CPRS scale consists of 65 items and is a clinically used instrument covering a wide range of psychiatric signs and symptoms. The first part of the scale (40 symptoms) is self-assessed by the individual her-/himself and the second (25 observed symptoms) is rated by the interviewer. CPRS assesses present psychiatric symptoms within a time frame of the last 3 days (80). Two subscales from CPRS were used to measure anxiety and depression. To measure anxiety the BSA-scale was used (81) (includes 10 variables, eight self-assessed and two observed) and to measure depression the MADRS-scale (82) was used (includes 10 variables, nine self-assessed and one observed) (83).

The individual items are rated on a 7-point scale (0-3) where 0 means absence of symptoms, 1 may indicate a potential pathological deviation but can also be considered as temporary feelings of undefined discomfort, 2 should mostly be considered as clearly pathological and 3 means an extreme degree of the symptom. A total score of ≥11 together with three or more subtotals of 2 points on the subscales is needed to meet criteria for anxiety and depression. Certain of the individual items are of great importance and must be rated (84). Remission of symptoms is defined as a score of 11 or less.

3.2.4 Reflective Lifeworld Research

The qualitative studies (**V** and **VI**) in this thesis have practised the reflective life-world research (RLR) approach (85). RLR is based on phenomenological ontology and

epistemology and the lifeworld perspective, with support from the philosophical texts of Edmund Husserl, Maurice Merleau-Ponty and Martin Heidegger. The phenomenon being explored and illuminated in these studies was men's and women's experiences of using AAS. From a phenomenological perspective, research should be meaning-orientated (86) and we must understand what our data means and its meaning. Guidelines for RLR (85) meet the criteria for studying individuals' experiences, i.e. openness and flexibility. An open but bridled attitude must be adopted during the process of data collection and analysis. The natural attitude is part of the everyday world and human existence, here everything is taken for granted (people and the outside world). This means that a researcher needs to slow down the process of understanding and step out of her/his natural attitude, be aware and adopt a reflecting attitude to be able to approach the phenomenon.

RLR is phenomenon-orientated throughout the whole process. Therefore, to begin with, in our studies, the interview transcripts were read several times in their entirety with an open mind to become familiar with the whole text and create a deep feeling and understanding. After this first step, the data was divided into smaller parts (words, sentences or longer pieces of text) in the search for meaning. Reflection and questioning were repeated until meanings were clustered together into patterns of understanding. Once the clusters were established, the meaning of the phenomenon slowly began to emerge and the pattern between the clusters and the essential meaning of the phenomenon became visible. By moving back and forward between the whole (interviews) and the parts (meaning of the data) it was finally possible to reconstruct a new whole (essential meaning) (85). Constituents (elements of meaning) were described, i.e. variations and nuances of the phenomenon on a more concrete level. The essence and its constituents are presented as a new whole in the results, illuminated by quotes.

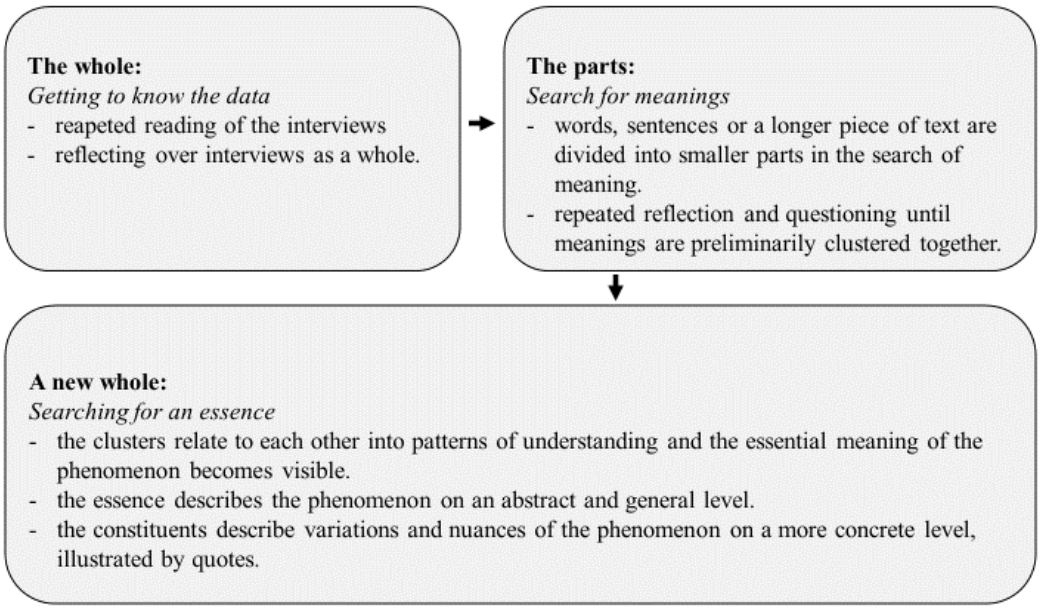

Figure 4. An overview of the process of analysis.

3.2.5 Ethical considerations

All studies conducted have received ethical approval. Studies **I** (ref. 2008/187-31), **IV** (2016/108-31), **V** and **VI** (ref. 2016/1762-31/5) were approved by the Regional Ethics Committee, Stockholm. Studies **II** and **III** (ref. 186/98) were approved by the Research Ethics Review Committee at Huddinge University Hospital, Stockholm. Participants (healthy volunteers) in **Study I** received financial remuneration.

The research conducted throughout this thesis adheres to the principles outlined in the Declaration of Helsinki (87) and is briefly commented upon in this section.

For understandable reasons it is difficult to obtain ethical permission to expose participants to potentially harmful amounts of AAS. In Sweden, most of the substances are only available on the black market, which makes it impossible to conduct experimental studies. The participants in most of our studies are "criminal" in the sense that under Swedish law, AAS are prohibited. Their use may result in fines, driving licence confiscation and for athlete's suspension from competitions.

In our previous studies, including **Studies II** and **III** in this thesis we have had an inclusion requirement that those involved should aim to end their use. However, this appeared to be ineffective as most of the participants continued their abuse (continuously positive in AAS tests) despite reporting a termination. Our conclusion is that it is even more important to

inform users about the risks associated with AAS use and to offer them assistance in withdrawing from their use.

Therefore, in **Studies IV, V and VI,** we excluded the requirement of AAS discontinuation and instead provided the participants with information about the risks of AAS use. They were also offered care and support based on their need of help. If it was found that the participants were in a need of more support than we could offer, the participants were forwarded to another appropriate care unit.

All individuals participated voluntarily and received oral and written information prior to the study. Participants were informed of the right to withdraw their participation at any time. They had to give written consent that they agreed to participate in the study.

4 RESULTS AND DISCUSSION

4.1 MOTIVES AND REASONS FOR AAS USE

4.1.1 Achieving the perfect body

Many motives were reported in our studies (**Studies II, III, V, VI**) for using AAS (Figure 5). Increase of muscle size, better performance and weight control were the most common motives. **Study V** showed that the women were striving for the perfect body and **Study VI** showed that men strived to achieve the perfect male body ideal. Women experienced their bodies as not being perfect enough which created anxiety. Men wanted to create the perfect physique based on the masculinity norm, which traditionally is muscular, strong, athletic and healthy.

The interviewees (**Studies V and VI**) described perfectionist traits showing their expectations of achieving the perfect body. Their bodies were sculpted by self-centred effort directed towards the desired body ideal. They were hard on themselves, driven by unhealthy ideals, sought confirmation, were self-critical and constantly saw their bodies' faults and shortcomings. Many females were involved in bodybuilding, and they competed (**Study II**, 87.5 % and **Study V**, 75 %) to a greater extent than men (Study **III**, 9 % and study **VI**, 60 %). Both men and women (**Studies V and VI**) stated that they need to take certain risks (use AAS) to have a realistic chance of meeting other people in the bodybuilding sport.

It is when a healthy striving gives way to self-imposed demands, self-critical evaluations of achievements and concerns about negative assessments (maladaptive perfectionism) that it can become unhealthy. The unhealthy part is not being able to accept oneself unless one is perfect, and constantly considering that one could do better (88). Perfectionism has increased in recent decades. This may be due to individualistic and materialistic environments with greater competition, higher demands and unrealistic expectations (89).

A bodybuilder's lifestyle is tough and time-consuming, and time needs to be set aside for daily routines. It is crucial to prioritise and follow one's busy food and exercise schedule to achieve set goals. There is an underlying stress in being disturbed in one's daily routines, and what is less important in everyday life has lower priority. To achieve their goals, they need to focus, which means that they have to be self-centred. Compared with men, women experienced a bad conscience because they put their families aside, while for men it was seen as necessary.

Figure 5. Motives for using AAS stated in the studies.

4.1.2 Body dissatisfaction

Both men and women in **Study V and VI** were dissatisfied with their bodies and strongly focused on increasing their muscles. In many parts of the world, body dissatisfaction appears to be a big concern (90) and a threat to psychological wellbeing (91). Individuals using AAS often have a strong body image fixation, a lower self-confidence about body appearance and are obsessed with training, diet and muscular appearance (37). The feeling of dissatisfaction persisted even though their muscles were getting bigger. The men compare themselves to men they consider as having the perfect male body and not to ordinary men. Men's and women's distorted body image made it difficult for them to perceive their own bodily changes realistically and to receive positive comments from others. To gauge their progress, and get a reliable picture of their development, they used scales, photographs and mirrors to help them, asked selected people for advice, used tape measures or tried on clothes. Now and then they experienced not looking handsome enough, or looking small, this made both men and women hide their bodies in large clothes, avoid attention and certain social situations.

Study	II ♀	IV ♀	III ♂	IV ♂
BMI	23.1 (19.8-29)	26.1 (22.3-29.6)	27.4 (21.2-33.7)	28.4 (22.8-34.6)

Table 2. Body mass index in Studies II-VI expressed in median (range).

Some men (**Study V**) described feeling ashamed over their bodies because they were not muscular enough and not wanting to show them in public. In our studies most of the individuals were muscular enough to be in the overweight range of the Body Mass Index value (see Table 2). In MD, hiding the body is described as a part of the symptomatology (32) because they sufferers symptoms of anxiety when exposed to environments where the body can be seen (30). However, when it comes to the women in **Study V,** they concealed their bodies due to fear of being exposed for illegal activity rather than fear of being judged for their appearance. Female bodybuilders probably tend to have the same risk of developing MD as men (92) but have been investigated to a very small extent (27).

4.1.3 Improving self-esteem/ self-confidence

Lack of self-esteem contributed to the experience of the body's imperfection. One of the reasons why the men in **Study III** used AAS was because they wanted to increase their self-esteem and/or improve their self-confidence (41 %). Feelings of inadequacy indicated that both men and women had lower self-esteem and self-confidence (**Studies V and VI**). Women learned while growing up that they had a higher value if performing well. It was important to be successful to counteract early fears of not being good enough. The men and women regulated their lack of self-esteem through self-control, discipline and performance, mainly achieved by following strict dietary and hard exercise routines. Their bodies were used as instruments to achieve goals and to receive confirmation. People recognised and looked up to them as bodybuilders, made them feel successful and strengthened their experience of being determined, disciplined and healthy.

Building one's body provided the opportunity to demonstrate skills and value which strengthened their feelings about themselves. They always gave their all in full, making great demands on themselves and doing nothing light-heartedly. Performance-based self-esteem

(PBSE) (93) is based on concerns of not being good enough and the results achieved are an important measure of ability (93, 94). It is a variant of low self-esteem based on the individual proving her/his human value through performance. Individuals with high PBSE are often ambitious and base their value on external factors such as success and personal status. Getting confirmation and/or respect for body development is vital for their wellbeing and becomes a compensation for their lack of self-esteem (93) but chasing achievements and positive feed-back from other people may lead to negative consequences such as stress and exhaustion (95).

Certain status was accorded them within their own group of bodybuilders depending on how well they attained their goals. This status was affected by how hard they worked and that they did not take the "easy" way of cheating by using a lot of AAS substances. They gained an identity, and the successes and the confirmation they received on account of it, led to satisfaction, better self-confidence and a positive self-image.
Identity is what characterises us and makes us unique and we use different tools to reach our ideal (96). Through the body we have the opportunity to create and transform our identity and self-image. Individualism places the responsibility on the individual her-/himself to seek her/his own way (96). International valuation surveys show that individualism and self-expression are highly valued in Sweden (97). The world becomes full of potential ways of living and acting, with which the individual can experiment.

4.1.4 Social background

Both men (**Study III**) and women (**Study II**) reported varied upbringings. The women in the interview study (**V**) described life-histories with eating disorders, bullying, negative comments about appearance, lack of recognition and lack of love. A large proportion of men (75%) in **Study III** reported troublesome life histories and only 1/3 were raised with both parents in their homes. They had their own experiences of drugs and/or alcohol, abusive and/or mentally ill parents, bullying, suicidal thoughts/attempts, difficulties at school, a parent's death or physical and mental abuse by a parent. The men expressed a poorer relationship with either or both parents than women did (**Studies II and III**). One study has previously described AAS users as being shown to come from severely disadvantaged family backgrounds with split families. They are described as more often exposed to physical, mental and drug abuse (98), but it is important to know that this is not a well-explored area. Male AAS users have also been described having a bad relationship to both parents (98), especially to their fathers (37). Parents' substance abuse is a predictor of harmful substance abuse in their off-spring (99).

4.1.5 Eating disorders

Almost every one of the women in the interview study **(V)** had earlier suffered from eating disorders. To manage their anxiety over physique, they started with strength training and through this they were able to keep their weight under control. Developing muscles requires adequate, monitored food intake. Diet increased their control over their bodies and reduced their anxiety. Unlike their previous experiences, eating became justified. But still body anxiety, occurred when routines around exercise or diet were disturbed. They feared not eating right or being able to handle a controlled diet, as has been described previously in female bodybuilders (27). A previous eating disorder made it easier for them to handle a strict diet. Sometimes food intake could get out of control with feelings of bodily collapse, creating body anxiety and resulting in compensatory training. Among the women in **Study II**, the desire for weight loss was prevalent, but only one woman described a history with an eating disorder. Eating disorders in men were not common to the same extent, there was only one man in **Study VI** and one in **Study III** who described a previous eating disorder problem. Eating disorders have been described in female bodybuilders (21, 27) and in male bodybuilders with MD (31, 100).

4.1.6 Initiating use of AAS

All the women except one in **Study II** had been introduced to AAS by a man in a close relationship. Before our finding, there was only one previous case report of a woman who was introduced to AAS use by her boyfriend (55). This finding was interesting to investigate further and was confirmed in our interview study where several women revealed that their first contact with AAS had also been through a man. This has now recently also been found in a Norwegian interview study (101). What also emerged in **Study II** was that the women were persuaded to start their use, and one of the women was probably even tricked into taking AAS substances.

Only 18 % of the males in **Study III** reported that they were influenced by a person close to them (trainers n=4, father n=3, friends n=3). Those influenced by a coach had the motive to get bigger and to enhance performance. Those who were influenced by their fathers had the motive to start with AAS because they were told that they were too small. One man wanted to fulfill his father's dream of becoming big and another man "wanted to regain power from the father who had abused him". The men who were influenced by a friend described a form of peer pressure of using AAS together. As in **Study III,** the influence of a peer seemed to be rare among male AAS users although such cases have been reported (22, 23, 102).

However, in our interview **Study VI,** group pressure is described between individuals. They do not want to lag behind, perform worse or have less physical development.

4.2 PATTERNS OF USE

4.2.1 AAS

Most of the participants (**II, III, IV**) practised stacking, i.e., they used several different AAS agents in cycles. The number of substances used during one and the same cycle differed between men and women. The women in **Studies II** and **IV** used on average 1.9 (1-2) and 2 (1-6) different AAS substances per cycle, respectively. The corresponding number in men (**Studies III and IV**) was higher, they used on average 3 (1–5) and 3 (range 1-7**)** substances, respectively. When comparing **Study II**, where data collection took place during 1998-2004 with **Study IV** from 2016-2017, women seem to have increased their number of different AAS substances. Today they use several different AAS substances during a cycle. However, caution must be exercised about drawing firm conclusions because of the small number of female participants. From the research interviews and from my clinical work at the Anti-Doping Hot-Line, I experience however that women are less afraid today of trying more and different AAS substances compared to about 15 years ago.

We saw that the majority of men (95 %) in **Study III** used injectable AAS formulations, which is nothing new (39, 103). The women in our studies did not use injections to the same extent at all (25 % of the women in **Study II** and 50 % of the women in **Study IV**). It is known since previously that women prefer oral administration (19). One reason that emerged in **Study V** was that women do not use injections to the same extent because they perceive the injection in itself as dirty and wrong. The author has a theory that another reason may be that tablets are perceived as less potent and thus causing fewer side effects.

Men's and women's first choice for use of AAS is somewhat different today compared with 15-20 years ago (see table 3). Testosterone was in **Study IV** (2016-2017) reported by 80 % of the men, this is also the most used substance among the callers (72 %) to the Anti-Doping Hot-Line. Nandrolone and Stanozolol were in the top 3 earlier and have now dropped into a fourth and fifth place but are still commonly used substances. After testosterone, trenbolone was the most popular AAS among men (**Study IV**), while in studies conducted 10–25 years ago this steroid was not on the top list of AAS (33, 40). The most popular AAS substance among women today (2016-2017) was oxandrolone, a substance we did not see in **Study II**.

But Stanozolol is still a popular substance among the top 3. In summary, men's first choice of AAS substances has changed to a greater extent.

	Women	Men
Studies II and III **(years 1998 - 2004)**	1. Stanozolol 2. Methenolone 3. Nandrolone	1. Nandrolone 2. Methandienone 3. Stanozolol
Study IV **(year 2016-2017)**	1. Oxandrolone 2. Stanozolol 3. Testosterone	1. Testosterone 2. Trenbolone 3. Drostanolone

Table 3. The most commonly reported AAS substances.

Men´s dosages (weekly doses) seem to be higher than 20 years ago (see table 4). It is already known that women use lower doses of AAS (19), which was also confirmed in our studies (**II** and **IV**). Men were using AAS more continuously today compared with 20 years ago (**Study III** compared to **IV**). This is in line with my clinical experience from the Anti-Doping Hot-Line.

	Women	Men
II and III **(years 1998 - 2004)**	225 (100 - 600)	546 (60 – 3789)
IV **(year 2016-2017)**	187 (70 – 900)	1368 (250 – 3800)

Table 4. Weekly dose of AAS expressed in mg- median (range).

An obvious reason for differences in use pattern may simply be the availability on the black market. I believe that another reason why the participants' first choice has changed during these 15-20 years may depend on AAS users' experiences of how to expose themselves to fewer side effects. On the other hand, in the interview studies, thoughts appeared of increasing the dose or switching to a more potent substance if muscle development was too slow **(Studies V and VI).** However, it may also be the case that women **(Study V)** consider reducing or discontinuing the dose of AAS if certain side effects occur. Maybe men are more prone to risk since their doses seem to be higher today. Both men **(Study VI)** and especially women **(Study V)** reported that they are careful and stick to lower doses as they do not want to cause side effects in their bodies.

Both men and women **(Studies II, III, IV)** used other drugs in addition to AAS. These drugs were other doping agents, medications to avoid or treat adverse effects of AAS, and/or drugs for fat loss. None of the female participants in **Study II** and six males in **Study III** reported using GH. In **Study IV** on the other hand GH was more commonly reported by women (50 %) compared with men (10 %) (OR = 6.8; CI; 1.0–46.8, P = 0.03). Dietary supplements were used among men to a greater extent 20 years ago (77 %) than today (36 %).

Approximately one third of those with pain related to training and AAS in **Study III** were using analgesic drugs, and 14% were using opioids. Previous studies have suggested that AAS may serve as a gateway to opioid addiction (104, 105). On the other hand, the use of analgesics (NSAIDs and opioids) is common in sports in general to reduce inflammation and pain after high training load (106, 107).

An ongoing use of narcotic agents/alcohol was reported by 38 % of the women in **Study II**, 67 % of the men in **Study III** and by 3% among individuals in **Study IV**. Frequencies of 30-50 % among men and 24 % in women have been reported in other studies (20, 33, 108). The lower number in **Study IV** could be due to not reporting or it may be that groups do differ from each other. A co-use of a narcotic may also be more common among help-seeking individuals. The co-use of narcotics can be considered a confounder and may partly explain the association between AAS and some of the side effects.

4.2.2 Detection

4.2.2.1 Testosterone and other AAS

On the WADA prohibited list, substances are divided into classes S1-9 based on pharmacological mechanism of action (68). The AAS substances (class S1) most identified in urine analysis were stanozolol (**Study II**) and nandrolone (**Studies III and IV**). Self-reported AAS substances did not completely match the substances found in urine. Individuals were positive on substances they did not report (**Studies II and IV**). This may be due to short half-lives (24 hours), contamination, memory default, long detection time (60, 109) or mislabelling. Around 40% of confiscated black market AAS are accurately labelled (110, 111). Nandrolone may be detectable in individuals up to a year after cessation due to the long half-life of the metabolite 19- norandrosteron (109). Other studies have found that self-reported and detected doping agents often do not corroborate for the reasons discussed above (27, 112). It has been reported that AAS have been found in dietary supplements (113, 114), and consequently athletes are advised not to use dietary supplements.

In **Study IV**, as expected, the men with a current use displayed higher median T/E, compared with those reporting intakes within the past year or no reported intake, respectively, ($P = 0.0001$). Of the current male testosterone users, 82 % exhibited T/E ratios > 4. That means that 18 % would escape a WADA accredited test, and 50 % would not be detected in a Drug Abuse Laboratory test using $T/E \geq 10$ as a cut-off.

The use of testosterone in women seems to be difficult to detect with the traditional T/E biomarker. Although total testosterone serum concentrations are elevated, the T/E ratio does not increase to the same extent as in men and does not reach the cut-off limit of 4. This is in agreement with another case study conducted in women (115). It is necessary to detect (trans-dermal) testosterone use in women since the high circulating total testosterone level (9.92 nmol/L) observed in the female participant using solely testosterone gel (70 mg/week) is in concentration ranges associated with performance-enhancing effects (9).

In **Study IV,** serum testosterone was quantified in women by both RIA and LC-MS/MS. The methods showed a strong correlation ($Rs = 0.98$, $P = 0.0003$), with significantly higher ($P= 0.03$) total testosterone concentrations with RIA (median 2.5 nmol/L) than with LC–MS/MS (median 0.26 nmol/L). Regarding women, the total testosterone concentration is often overestimated when using antibody detection methods due to cross-reactivity (116, 117) which corroborates with our results in **Study IV**.

The men´s testosterone values were quantified only by RIA method as it delivers reliable values, more consistent with results from LC-MS/MS (118, 119). However, the RIA method employed in **Study IV** cannot quantify values higher than 50 nmol/L. Subsequently, we could not determine absolute concentrations in men who had injected testosterone within the last days. That serum concentrations reach 100 nmol/L after testosterone enanthate injections has been seen in previous studies in volunteers (120).

For the other ABP ratios no statistically significant differences between the participants with a current testosterone use and previous use were observed. This indicate that T/E is the major ratio that triggers a confirmatory Gas chromatography-combustion-isotope-ratio mass spectrometry (GC-C-IRMS) analysis which was also concluded in an administration study in men (121).

4.2.2.2 Other doping substances (S2-S9)

Growth factors and Peptide hormones (S2) were analysed only in individuals reporting current or a recent use within the past 2 months in **Study IV**. Detection of recombinant GH with Isoform GH test resulted in negative test results. This was expected since the detection window of GH is short (<24 hours) (122). There was one positive test on Ibutamoren (MK-677). Ibutamoren was taken by nasal drops eight weeks earlier according to the participants' statement. Ibutamoren is the most commonly detected GH-releasing secretagogue in WADA statistics (123). Hormone and metabolic modulators (S4) and stimulants (S6) were detected in 39% and 27% of the samples, respectively. Diuretics (S5), cannabinoids (S8), and glucocorticoids (S9) were detected in <10% of the samples. Beta-agonists (S3) and narcotics (S7) were not detected in any of the participants.

4.3 SYMPTOMS AND SIDE EFFECTS OF AAS USE

Supraphysiological doses of AAS increase the risk for side effects and are associated with many side effects that can impact many organ systems. It can be difficult to establish a direct association between AAS substances and side effects, because of interactions between multiple co-existing factors in each individual. The individual may overestimate or underestimate her/his own experience, which affects the reporting. Time is also important in this context - how long ago something happened.

4.3.1 Somatic side effects

The most common reported somatic side effects in men (**Study III**) were acne, gynaecomastia and decreased libido (table 5). All women using AAS (**Study II**) reported at

least some of the classical side effects such as clitoral enlargement and voice change (table 5). In addition to the traditionally reported side effects of AAS, 86 % in **Study III** experienced pain in some form. Most common was pain in the joints, the back, knees, shoulders, elbow, and wrists that was related to hard training loads (67 %) during AAS use. There were also individuals who experienced pain from their side effects such as gynaecomastia and acne (27 %).

Women (Study II)	**Men (Study III)**
1. Clitoral enlargement	1. Acne
2. Voice change	2. Gynaecomastia
3. Menstrual disorder	3. Potency problems
4. Body hair growth	4. Stretch marks
5. Acne	**5.** Arrhythmia and chest pain

Table 5. Most reported somatic side effects in women (Study II) and in men (Study III).

4.3.1.1 Cardiovascular side effects

In our study (**IV**), HCT and Hb values are shown to be high in male current users. This is in agreement with an earlier study where they also observed that a six month cessation of AAS lowered haematological values (65). AAS-induced high HCT may be a risk factor for thrombotic events (59). None of the women using AAS reached a similarly high HCT value and their Hb values were within the normal range (**Studies II and IV**). This gender difference may simply be due to the lower AAS doses used by women. However, when transgender men received supra-physiological doses of testosterone, increased HCT values above 50 % were rarely found (124). Subsequently, high HCT and Hb values induced by AAS may be predominantly a male problem.

Our data in **Study I (**with healthy individuals) showed that even a single dose of the AAS substance nandrolone increased the total cholesterol level in serum. This was also reflected by an increase in HMGCR mRNA and an increase in ApoB. This has been shown before but instead of nandrolone the participants were then given testosterone (62). A disturbed cholesterol profile has been found in a previous study in AAS users (same study population

as in Study **III** (60). This supports the conclusion that AAS use is a risk factor for cardiovascular diseases even in moderate, intermittent or temporary use.
In the healthy men (**Study I**) and among women using AAS (**Study II**) we did not see any significant changes in HDL and LDL. The lipid profile is highly dependent not only on dose and type of AAS but also on age, diet, exercise, genetics etc. (62, 120, 125, 126).

Mild hypertension is common in AAS users (59). The systolic and diastolic blood pressures observed in both men and women in **Study IV** were higher than measured among AAS users in other studies (including **Study III**). There were no significant differences between the groups (current, recent and previous users) which indicates that high blood pressure may have other causes. Participants with high blood pressure in **Study III** also displayed elevated HCT and Hb values (unpublished data). One reason may be the white coat syndrome, a blood pressure level above the normal range due to anxiety from being in a clinical setting. The blood pressure in **Study IV** was measured on only one occasion which may be a weakness.

Cardiovascular problems were experienced by 30 % of the individuals in **Study III**, and they reported symptoms such as irregular heart rhythm and chest pain. Cardiovascular problems are normally not self-reported to such a high degree by the users themselves (20). The reason for the high numbers in **Study III** (30 %) may be that a specific question regarding cardiovascular problems was directed to the participants by the study nurse. It is also possible that the individuals included in this study were more concerned about their side effects than AAS users in general, since they had contacted health care (i.e. selection bias). Severe heart disease was described as one of the reasons why several of the men in **Study VI** stopped using AAS. A predominant proportion of participants in **Study III** showed a distinct thickening of the septum and posterior wall (≥ 10mm) (unpublished result-see figure 6). Individuals who discontinued their AAS use were associated with a thinner septum wall in connection with normalised gonadotropin levels ($p=0.04$).

All in all, high HCT, disturbed cholesterol profile and high blood pressure together increase the risk of cardiovascular disease. In fact a study has shown an association to cardiovascular diseases in a group of competing powerlifters, with 4.6 times higher risk of death (127). A 10-fold premature mortality has been noted after ten years of follow-up in AAS patients, where one of the main causes of death being cardiovascular disease (128).

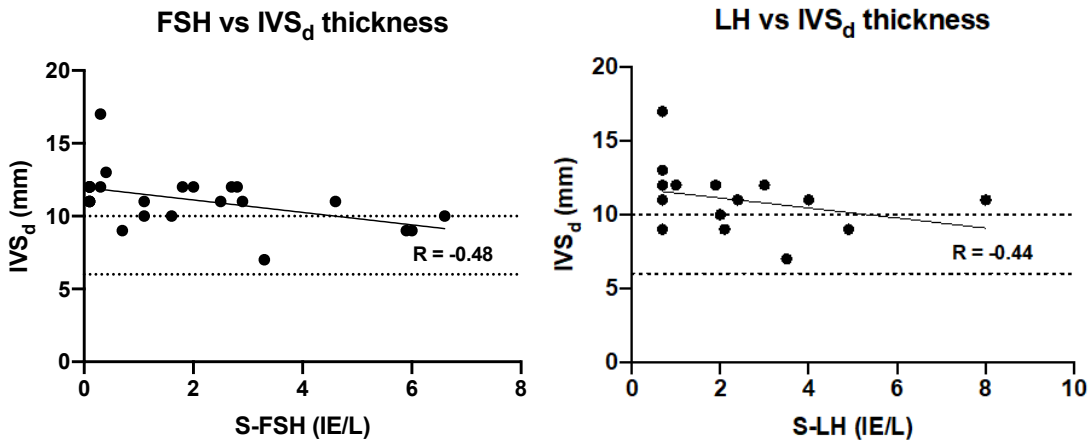

Figure 6. Correlation plots of FSH (left) and LH (right) against IVSd. The interval between the dotted lines represents normal values. The solid line in each plot represents the regression of the y-variable for AAS-abusers (black dots) against increasing.

4.3.1.2 Endocrine side effects

We have earlier shown that the population in **Study III** had low testosterone levels at inclusion (63%), with a value below 12 nmol/L (65). Since many of the individuals reported potency problems and depression (**Study III**), it may be so that these symptoms correspond to a clinical diagnosis of hypogonadism. This means symptoms of testosterone deficiency in combination with low testosterone levels, since testosterone levels over 12 nmol/L are considered as being normal (129). Androgenic steroid-induced hypogonadism is associated with depressive symptoms (39, 130). It is well known that AAS users have a disturbed endocrine profile (60, 131) that is repressed for longer periods of time (60). Our research showed that even one single dose of nandrolone affected LH and FSH levels (**Study I)** and that these hormones gradually increased with cessation time (**Study IV**).

4.3.2 Psychiatric symptoms and side effects

4.3.2.1 Aggression

The women in **Studies II and V** experienced mood changes, i.e. irritation and- aggression but not at all to the same extent as men. Aggression during AAS use was the most common self-reported psychiatric symptom (71 %) among the men in **Study III**. Many of them were using other drugs (42%) at the same time. The men in **Study VI** were convinced that aggression was associated with the use of narcotic agents in combination with AAS. Aggressiveness has been shown in rats pre-treated with nandrolone when given amphetamine (132). Controlled studies, however, failed to find an association when supra-physiological doses of AAS were administered to healthy men (133, 134).

It has been reported that individuals who are using or are intending to use AAS have significantly higher aggressive tendencies prior to use (135, 136). In our **Study III**, however, only 9 % reported aggressive feelings prior to starting AAS use.

Individuals with a PD were more likely to self-report aggression (81 %), but they also used narcotic agents and/or alcohol to a greater extent (**Study III**). A relationship between PD and aggression is well-known in non-AAS users and individuals with PD have been reported to be predisposed to aggressive or self-destructive behaviours when under stressful conditions (137). Our results showed that individuals with a SCID II diagnosis showed a significantly increased risk of self-reporting aggressive feelings/behaviours (Odds Ratio (OR) = 4.9; Confidence Interval (CI) 0.99–25, p = 0.04).
Knowledge is scarce on the prevalence of PD in AAS users. Other studies have found a higher prevalence of psychiatric diagnoses among AAS users than in non-users (112, 138). Whether these psychiatric disorders are primarily induced by AAS or other concomitant drug use or if they are due to pre-existing psychiatric pathology is not known. In conclusion, our findings are in line with previous studies suggesting that PD and the co-use of narcotics may partly explain the association between AAS and aggressive behaviours (139).

4.3.2.2 Violence and criminality

The men described frequently ended up fighting and 45 % self-reported violence in **Study III**. The violence was often directed towards other people during the time they were using AAS. The abuse was often directed to the person they were living with (girlfriend or wife), and some described being drawn to violent situations. Relatives' calls to the Anti-Doping Hot-Line describe violence against persons or things, throwing things around, and roid rage (40). Only two individuals stated that they had been violent before they started with AAS. The relationship between PD and violence (140) is well-known in non-AAS users. In our study, violence was not more prevalent in AAS users with PD. The men in the interview study **(VI)** thought that people who do not use AAS looked at them as dangerous, aggressive and violent and were frustrated over the fact that media had largely contributed to creating this image of them.

The participants in **Study III** were engaged in "criminal" activities (43 %) and many (34 %) had been in contact with the police for assault, peddling of AAS, theft or robbery. A significantly increased risk for criminality was found among individuals with a PD (OR =

6.5, CI 95; 1–39, p = 0.03). AAS users have been found to be more often involved in crimes (128), to have assaulted and/or threatened their female partners and used alcohol and drugs to a greater extent than non-users (98).

4.3.2.3 Depression and anxiety

In Study **III,** the second most reported psychiatric symptom was depression (54 %), and it was also the most common SCID I diagnosis (41 %). Of the people who received a SCID 1 diagnosis for depression, 81 % also met the criteria for depression rated in the MADRS scale. These two clinically used instruments strengthen the men's experience of being depressed. At inclusion, 47 % of the individuals rated a score > 11 on the subscales for MADRS. A numerical, though not statistically significant, decrease in the MADRS scores from inclusion to the six-month follow-up suggests that feelings of depression diminished over time. A high score of anxiety was rated by 69 % of the individuals on the BSA-scale. A high self-reported lifetime prevalence of seeking professional expertise for psychiatric problems such as depression and anxiety has been described (141). There was a significant decrease in the BSA score from inclusion to the follow-up ($p < 0.01$, Figure 2, n = 19). This might be due to the AAS cessation itself or to fewer concerns about side effects.

4.3.2.4 Suicidality

One striking result in **Study III** was the high number of reported suicidal thoughts and attempts during AAS use (n=17, 30 %). AAS users diagnosed with PD were at a five times increased risk of a (self-reported) suicide attempt and/or suicidal thoughts. The incidence of suicidal attempts/thoughts may be higher in AAS users (55, 138, 142) but has been investigated to a very small extent. Apart from AAS use as such, suicidality may be linked to PD (143, 144), or narcotic use or other social background factors (144). Experiences of parental divorce as children or adolescents or abusive parents during childhood also constitute an elevated risk for lifetime suicide attempts (145).

4.3.3 Managing side effects

AAS users describe different ways to deal with side effects. Our research shows that side effects were suppressed, prevented, reduced or avoided by different strategies.

4.3.3.1 Concern for side effects

All the men and women in **Studies II, III, V and VI** expressed concerns about side effects. This was the main reason for participants in **Studies II and III** to contact the Anti-Doping Hot-Line. Concerns about perceived negative effects of AAS are also the most common

reason why other AAS users contact the Anti-Doping Hot-Line (40). The duration of AAS use before getting in contact with the Anti-Doping Hot-Line for women (**Study II**) was between 7 weeks and 2 years (mean 58 weeks) and for men (**Study III**) it varied between 0.5-17 years (mean 5.2 years). Most men reported six to ten side effects (**Study III**). Men in **Study VI** who explicitly described that they were more attentive to the body's signals often used AAS in lower doses. Most of the women reported five side effects, and they were more prone to contact health-care givers at an earlier stage and experienced side effects even at low doses (**Studies II, V**), which probably could be explained by the negative and bothering side effects women experienced. In general, unwanted side effects are experienced more by women (21) probably because women have lower testosterone levels and are more sensitive to exogenous administration of steroidal agents (146). Women probably uses lower doses and fewer AAS agents to minimise the negative side effects of AAS.

In **Study III and VI** it was evident that the majority of men had plans to continue despite side effects and they prefer to self-medicate rather than end their use of AAS, the same phenomenon has also been discussed by (20, 39, 147). This illustrates the fact that there is a real challenge involved in getting AAS users to stop their doping even though they experience side effects.

4.3.3.2 Underestimation of side effects

Both men and women in the interview studies (**V and VI**) underestimated their side effects. Men stated that they were not bothered by their side effects. Women, on the other hand, kept an eye out for any side effects in order to make changes in their AAS use to counteract them. Their concern about side effects decreased when serious side effects did not show up and to be able to consider ending their use of AAS, they needed proof that the side effects actually were caused by AAS. The men declared that even though they had stopped using AAS due to acute and serious illness, they were still not sure if the side effects were caused by AAS. Previous research has shown that both men and women tend to underestimate and neglect the side effects of AAS (27, 147, 148) but they are nonetheless concerned about harmful effects on health (39).

4.3.3.3 Balancing side effects

To avoid masculinising side effects and over-large muscles, the intake of AAS needs to be balanced. Women are uncertain about being able to handle this balancing act and live with the fear of losing their femininity. Women have an inner limit (**Study V**) for acceptable side

effects, so they struggle to maintain the balance between desirable muscle development and acceptable side effects. Not being able to get pregnant, and permanent side effects such as clitoral enlargement, increased body hair or a deeper voice frighten them. Women contacting the Anti-Doping Hot-Line describe having experienced side effects from using AAS only once, so it is understandable that worries exist for women about side effects. Women interviewees related that it was common to be led by a man who gave them advice based on how men use AAS (**Studies II and V**). But the women in **Study V** were critical to this because men do not know how AAS work in the female body. Overall, they were critical to all information they obtained or received because they did not want to be deceived into making the wrong choices. They said that it would have been easier to avoid side effects if one knew which information is authentic. Today, there is almost no honest and fact-based information specifically aimed at women (**Studies II, V**) although women are more vulnerable to side effects (19, 27, 101).

Women are probably more aware today than 15-20 years ago, since it is easier now to find information online. They are probably also more aware of how women's bodies can be transformed by using AAS and they have learnt to question information because it is important for them to maintain their femininity. Norms for femininity make it impossible to discuss women's use openly. People's views on femininity are affected by traditions and societal norms in terms of appearance and appropriate clothing. Women with large muscles are questioned by others. Existing standards of femininity cast a permanent shadow over existence. A man, on the other hand, does not have the same worries about losing masculinity, instead men use AAS to gain masculinity and side effects are often experienced only temporarily.

4.3.3.4 Hiding side effects

Knowledge about AAS and how to use the substances is required in order to hide the use of AAS from others. The reason why men and women try to hide their use of AAS is partly due to their concern about consequences because AAS use is illegal in Sweden and partly because they avoid being treated unfairly by other people. The fear of this secret use being revealed is constant, if the physical changes and side effects were to be noticed by others and lead to social consequences and penalties. They hide their physical development and disguising visible and invisible side effects e.g. they hide their bodies in larger clothes and/or try to avoid doping tests. The secret use of AAS requires men and women to live with lies. Men lie so as not to reveal their AAS use because they are often treated with a condescending and judgemental attitude for their lifestyle. Women are concealing their bodies due to fear of

being exposed for illegal activity rather than fear of being judged for their appearance. Both men and women limit their social context to avoid being questioned.

Men only contact healthcare when it is absolutely necessary and then choose not to be completely truthful about their use of AAS. They may also be afraid of telling the truth in case they do not get any help for their side effects. They experience a strong sense of trust and security when they meet a "factual", honest and non-judgemental physician. It is easier to be honest and open to people who do not judge. They also then feel more receptive to information about their AAS use. According to the men's experience, there is a general perception that all AAS users show aggressive behaviour (**Study VI**). Their body size can also be experienced as intimidating by others (149), and this can affect the meeting and treatment between patients and the physicians, which is another reason to try to hide the use of AAS.

4.3.3.5 Help-seeking behavior

Another way to deal with side effects is to seek medical help. The men in **Study VI** would have preferred to use AAS legally under the direct supervision of a knowledgeable physician. This would help them to monitor their health and avoid and reduce their concern about side effects. Other AAS users have stated that they would like to have routine health and laboratory checks to monitor their health while using AAS (39). Only eleven men in **Study III** wanted professional help to terminate their AAS use. Six men made their own decisions to stop using AAS, the remaining men experienced demands from relatives (n=3) or from their physicians (n=2). Only 25 % completed their participation throughout the study. The number of dropouts in the Studies **II and III** was high, despite the fact that they reported several side effects. It may have been that they felt calmer and less worried about their perceived side effects when they received a health examination and met a physician and nurse with specialist knowledge in doping. It may have been the case that the men in **Study III** primarily wanted a medical check-up. Quitting their use was not their primary concern. Maybe some did not want to give up AAS but wanted to know if their side effects were dangerous. Once they received reassuring answers, their anxiety subsided, and they did not feel the need to continue in the study. The BSA-score that measured anxiety also reinforces this hypothesis since the participants' anxiety decreased from inclusion to the six-month follow-up. One reason given for terminating their participation prematurely was that they felt good or wanted to continue their use of AAS, and 32 % ended their participation within six months. This, together with the requirement that the participants must have stopped using AAS when entering the study, may have contributed to the high proportion of dropouts.

The men in **Study VI** had negative experiences from the past when they were help-seeking. A low trust in physicians' knowledge may stop AAS users from seeking help for their AAS-related problems (22, 150). Similar reasoning has been expressed by AAS users contacting the Anti-Doping Hot-Line.

Negative experiences of dealing with hospital staff may affect the individual´s choice of seeking medical care. As for other people AAS users keep their emotions to themselves if not receiving enough information or if they are not treated with respect (151). Instead they seek medical advice through online steroid fora which may result in incorrect advice. The men in our **Study VI** thought that it was the individual´s own choice to use AAS and they did not want to be questioned about this. Rules and regulations are questioned in online steroid fora, and this neo-liberal attitude and acceptance lead to a "normalisation" of AAS use that challenges norms and regulations (152). Today, it is possible to do online health checks, an alternative to having to seek assistance physically from a physician.

4.3.3.6 If AAS use needs to be discontinued

If a person's AAS use is revealed to others or if the body is let down by illness, that person's existence may be jeopardised (**Study VI**). When demands are made to return to a "normal life" by close relationships or by society at large, these men's freedom is restricted. The demands may be overpowering, and it may be difficult to carry on their lives as usual. Both men and women (**Study V and VI**) used their bodies as an instrument to raise their self-confidence and their self-esteem. The context of meaning may change when something with which we handle the world breaks down, such as a tool, in this case "the body" (153). Existential free choices are limited in the event of illness. Having to quit one´s lifestyle may be experienced as having to leave one´s body physically, mentally and socially. It may feel like the end of life. Existence is what frightens us when we are left to ourselves (154).

The role of the perfect male ideal is maintained in interaction with people around and kept alive through other people's confirmation, acceptance and integrity (**Study VI**). If the use of AAS must be stopped, the social role that men have achieved may be affected and they may experience that their identity and authenticity are being questioned. The social role that men have built up and that has been shown to the world (155) can easily be destroyed, shattered by adversity.

4.4 METODOLOGICAL CONSIDERATIONS

In **Study I**, whole blood was used as a surrogate model for HMGCR mRNA expression and not liver tissue, since for obvious reasons taking a liver biopsy is not a practical solution. mRNA in blood may not always reflect the mRNA expression profile of liver enzymes (156).

The data in **Studies II** and **III** was collected around 20 years ago. However, as the AAS use pattern appears to be to some extent similar in Sweden today (result from Study IV and daily communication with AAS users via the Anti-Doping Hot-Line), although there is a tendency towards continuous AAS use rather than AAS use in cycles, we believe that the results are still representative. A further limitation is that the oral interview with specific directed questions may overestimate the frequencies of adverse effects. But it could also be considered a strength since the individuals may be more willing to open up, disclose their problems and provide information they normally do not intend to report.

The low number of female participants in **Study IV** made it impossible to make statistical calculations. Therefore, the gender-comparative results should be interpreted with caution. Another limitation with our study design is that the group division based on "washout" periods may depend on administration routes, different doses, and stacking practice in cycles. It would also have been interesting to have a complete history of the participant's use of AAS beyond a year ago to know if they had used the substances that were detected in doping test. Moreover, it would have been a strength if repeated samples had been collected to follow the different biomarkers longitudinally in each individual.

In-depth interviews in **Studies V** and **VI** with support for reflection have contributed to a truthful material since substantive meanings have emerged. One weakness of the method is that it is time-consuming and requires knowledge in interview technique but in order to gain a deeper understanding, in-depth interviews as a method have been shown to be a strength.

A weakness in the study was that I had experience of talking with many AAS users. This had given me some prior knowledge and understanding. It was important not to let my experiences take over during data collection and analysis to maintain an openness and to be observant and sensitive to the informant's lifeworld. Through the research process, the whole research team have together reflected their pre-understanding and questioned their own and each other´s assumptions and thoughts and thus stimulated self-reflection.

5 GENERAL DISCUSSION

The results from all these studies shows that there is a link between AAS and side effects, somatically, psychiatrically and also psychosocially. Even though the use of AAS is considered to be a health problem, there is no comprehensive widespread information about the risks. This highlights the importance of preventative measures, in both sports communities and the whole of society. The overall knowledge in society about women's use of AAS is very low today, and there is almost no honest and fact-based information specifically aimed at women although women are more vulnerable to side effects. Therefore, gender needs to be considered when disseminating information.

To be able to discover and prevent the use of AAS, reliable detecting methods are also needed. A clinical suspicion of AAS use must be verified by analysis. An early diagnosis increases the possibility of adequate treatment for the individual patient. An exogenous synthetic AAS is easier to detect while testosterone can be more difficult. **Study IV** showed that as many as 50% of the testosterone users could have escaped a doping test. In Sweden, the limit for a positive doping test in the community (157) is set to a T/E ratio above 10. The women reporting trans-dermal use all had difficulty reaching T/E >4, which is the limit for athletes, although serum levels showed high values. Most AAS users are not elite athletes, therefore they are not followed by ABP. Testosterone seems to be the most commonly used substance among men **(Study IV) (**data from Anti-Doping Hot-Line). This indicates that it is "safer" for AAS users to use only testosterone as a doping agent if they want to escape a doping test. Our results highlight a need to increase the sensitivity of the methods employed at the abuse and forensic laboratories today. The inclusion of additional urinary androgen metabolites may be helpful. Moreover, additional matrixes, including blood and saliva (158), may be used for testosterone detection.

The participants described concerns for side effects which also constitute the most common reason for contacting the Anti-Doping Hot-Line. The BSA-scale **(Study III)** showed that the participant's anxiety decreased from inclusion to the six-month follow-up. I think this indicates that professional help in the form of medical health examinations reduced the individuals concern for side effects. But men and women in **Studies V and VI** turned out to be fearful of revealing their use of AAS because often they are often judged by others for their lifestyle. This and earlier negative experiences from contact with healthcare professionals may be one of the reasons why they do not want to seek help. But it could also be that they were afraid of not getting help with their problems or were fearful of social consequences such as being reported to the police. The participants wished to meet a

“factual”, honest and non-judgemental physician. They wished to meet a physician with whom they could experience a strong sense of trust and security, a person they could be honest and open to. Then they would be more receptive to information about their AAS use. If physicians were to be more open and flexible in their attitude towards AAS users, they would probably find it easier to reach this patient group. A “good” contact with healthcare personnel may lead to fewer side effects, not having to lie or self-medicate and hopefully a way towards ending the use of AAS.

It is through our bodies that we humans relate to the outside world. Other people´s views on our bodies may arouse self-criticism and feelings of inadequacy (159). The law in Sweden imposes obstacles since use is illegal. Despite this, the law does not stop people from achieving change. Striving for positive self-perception is a driving force for change. A new identity and social appreciation benefit a person´s self-perception (160).

6 CONCLUSIONS

Conclusions Studies I-VI:

I) One single dose of nandrolone increases the total cholesterol level in serum which is also reflected by an increase in HMGCR mRNA and increase in ApoB. This indicates that AAS could be a risk factor for cardiovascular disease even in moderate, intermittent or temporary use.

II) Women used fewer doping agents and smaller doses than men and were more prone to contact health care at an earlier stage. Women had been introduced to AAS by a man in a close relationship.

III) AAS users with a PD diagnosis showed a significantly increased risk of self-reporting aggressive feelings/behaviours, suicidal thoughts/attempts and criminality. A high score of anxiety was rated on the BSA-scale, which decreased significantly from inclusion to the follow-up.

IV) In women the T/E ratio could not detect the current use of testosterone gel, despite elevated testosterone levels in serum. Changes in gonadotropins and haematological parameters were associated with the time of the last AAS intake in men while they were within the normal range for women.

V) Achieving the perfect body involves existential challenges. Body dissatisfaction creates anxiety which is mastered by hard training, strict diet and the use of AAS. Lack of self-esteem contributes to the experience of the body´s imperfection. The experience of succeeding through their achievements creates a sense of pride, which is the driving force, triggering tension between suffering and success. It is an arduous endeavour for women to balance the substances' side effects with the desired femininity. The use of AAS also means living with lies and the fear of being discovered, because AAS are illegal.

VI) By using AAS, men strive towards a muscular, strong and athletic ideal. Self-imposed demands, self-discipline and performance accelerate male physical development. The new self-identity stimulates respect by being impressive, prominent and dominant. An identity is created and shaped, which over time leads to self-confidence and a positive self-image. The perfect male body ideal thus attained is fragile from both an existential and a biological perspective. The perfect self-image can easily be shattered by adversity. Existence may be jeopardised if the use of AAS is revealed to others or if the body is let down by illness.

7 POINTS OF PERSPECTIVE

There are risks involved in doping; the individuals themselves are at risk from side effects, and relatives may also suffer from the consequences of side effects such as mood swings and violence (**Study III**) or self-preoccupation and lies (**Studies V and VI**). No one has investigated how relatives are affected by living close to a person using AAS. This is an important field of research that needs to be explored. Semi-structured interviews with a lifeworld perspective would be suited to getting deeper knowledge.

The short-term medical effects of AAS are more investigated than the long-term. Long-term effects are scarce and often retrospectively based on self-reports or the assumption that certain groups of athletes (i.e. weightlifters) used AAS during their active career. Long-term studies are essential and necessary to learn about health risks associated with AAS. Now, however, people who started their use in the 1980s are beginning to reach middle age and their experience of long-term effects can be examined (29, 161). The data in **Studies II** and **III** were collected almost 20 years ago and it would be interesting to carry out follow-up studies on this cohort.

In the qualitative studies in this thesis, life world interviews have been chosen as the method for data collection. In future research, it would be interesting to ask the informants to write diaries to bring further understanding of daily life and bring forward aspects that the women were not able to put into words in the interviews. In a future research project, this can contribute new knowledge to the field.

8 ACKNOWLEDGEMENTS

Den här avhandlingen hade inte varit möjlig utan många människors hjälp och stöd. Det har varit en fantastiskt rolig resa. Forskningen har gett mig ett vidare perspektiv, det har varit stimulerande och intressant men det har också fått mig att utvecklas i mitt yrke. Jag har mött otroligt många fantastiska och engagerade människor, jag vill särskilt börja med att tacka mina handledare.

Lena Ekström, min huvudhandledare. Jag kan inte med ord beskriva vilken bra handledare du är. Tack för att du tog dig an mig som doktorand och för att du delat med dig av din breda kunskap, engagemang och erfarenhet. Tack för att din dörr alltid har varit öppen, ditt tålamod med mig och för ditt ödmjuka sätt. Du har ett brinnande engagemang och ditt ansikte lyser alltid upp när du pratar om ditt ämne, jag är fascinerad av hur dedikerad du är. Jag kunde verkligen inte ha fått en bättre huvudhandledare!

Marja-Liisa Dahl, tack för att du gav mig den här möjligheten. Tack för att du alltid har hittat tid för mig, varit en god lyssnare, stöttat mig och för att du varit så noggrann.

Veronica Vicente, du har öppnat en ny värld för mig och introducerat mig till nya kontakter. Din erfarenhet, färdigheter och sociala nätverk har varit ovärderligt. Din egenskap att kunna förklara på ett enkelt sätt är fenomenal. Tack för att du hela tiden har funnits där för mig, lyssnat och stöttat!

Mikael Lehtihet, endast 4 % bihandledare på papper men med ett 100% engagemang. Du är aldrig besvärad fast man ringer med de mest konstiga frågor på de mest udda tiderna. Alltid med en stor portion optimism som förmedlar att man inte ska ge upp. Ett exempel på det är när vi för tredje gången fick tillbaka artikel III med reviewernas kommentarer, då sade du ”det var inte så farligt, det kunde varit värre”. Tänk att den blev publicerad till slut och tack för all pushning framåt genom de här åren.

Jenny Schulze, **min mentor**, tack för kunskap och inspiration.

Mina medförfattare, det har varit ett nöje att få skriva med er, jag hoppas att jag får fler möjligheter till det i framtiden, tack för att ni har delat med er av er värdefulla kunskap, **Alexander Andersson, Magnus Ericsson, Margaretha Ekebergh, Anders Rane, Nina Gårevik och Christian Möller.**

Ett särskilt tack till före detta/nuvarande kollegor och doktorandkollegor som jag delat den här tiden med; Camilla Linder, för fantastisk undervisning och förtroliga samtal,

Jenny Mullen, **Michel Arvidsson, Johan Holm** och **Madeleine Pettersson Bergstrand** för kunskap och givande samtal, **Anders Rane** tack för dina vetenskapliga råd och för att du anställde mig på Dopingjouren, **Ann-Mari Thurelius**, för att du introducerade mig till ”dopningsvärlden”, **Yvonne Elliman** för hjälp med utskrifter av intervjuer, **Pamela Grönkvist**, för din alltid hjälpande hand, **Alexander Andersson** för hjälp med analyser och undervisning, **Kim Pettersson Bohlin** för hjälp med analyser, **Nina Gårevik** för att du inspirerade mig till att börja forska och för din förmåga att se igenom problem och se det positiva i det mesta, **Susanne Broström** för ditt stöd och för många skratt, **Michèle Masquelier** för att du inspirerar. Tack till **Klinisk farmakologi**, en bra plats på jorden fylld med kunskap. Ett extra tack till alla på **Dopinglabbet** för att jag fått ta del av er kunskap, för fredagsfrukostar och trevliga pratstunder.

Min vän **Esmeralda Iversjö**, tack för att du stöttat mig igenom den här processen genom att alltid finnas där, nu hoppas jag på fler fikastunder! Tack **Johan** och **Inger Moge** för fin vänskap och för att ni alltid ställer upp för oss och barnen. Tack **Anita Nykvist**, för lång vänskap och för administrativa utryckningar.

Och slutligen all kärlek till **min familj** som alltid har stått bakom mig, stöttande och omtänksamma. Jag är så glad över att ni alla finns i mitt liv. Tack **mamma** och **pappa** för att ni alltid har trott på mig och lagt grunden till att jag har velat studera, tack för att ni har fått mig att tro på mig själv. **Madeleine**, min fantastiska *lillasyster*, vi delar medgångar och motgångar, tack för att du alltid finns där för mig! **Neo** och **Nellie,** mina fina syskonbarn, jag är så glad att få vara moster till er och det ska bli roligt att få följa era vägval. Min svärmor, **Mona**, som stöttat mig genom detta men försvunnit ifrån oss alldeles för tidigt. **Janne** och **Gunilla**, **Sara**, tack för avkopplande och trevliga stunder, de har varit värdefulla!

Mina underbara barn, Melwin tack för din omtänksamhet och för ditt tålamod, **Hannah**, tack för våra stunder med skratt och för de två illustrationerna du gjorde till avhandlingen (fig.1 och 5). **Jens**, **min fantastiska man**, min bästa vän, mitt viktigaste stöd i livet. Du ger mig alltid ett nytt perspektiv på tillvaron. Varje dag blir en bättre dag när du finns vid min sida. Nu väntar mer tid för fiske, jag lovar härmed att använda det där fiskespöet och följa med ut i båten…iallafall några gånger 😊. Utan er hade detta inte varit möjligt, jag älskar er ändlöst och mer ♥

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